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Computer-Assisted Electrocardiographic Analysis System: Methodology and Potential Application to Cardiovascular Toxicology

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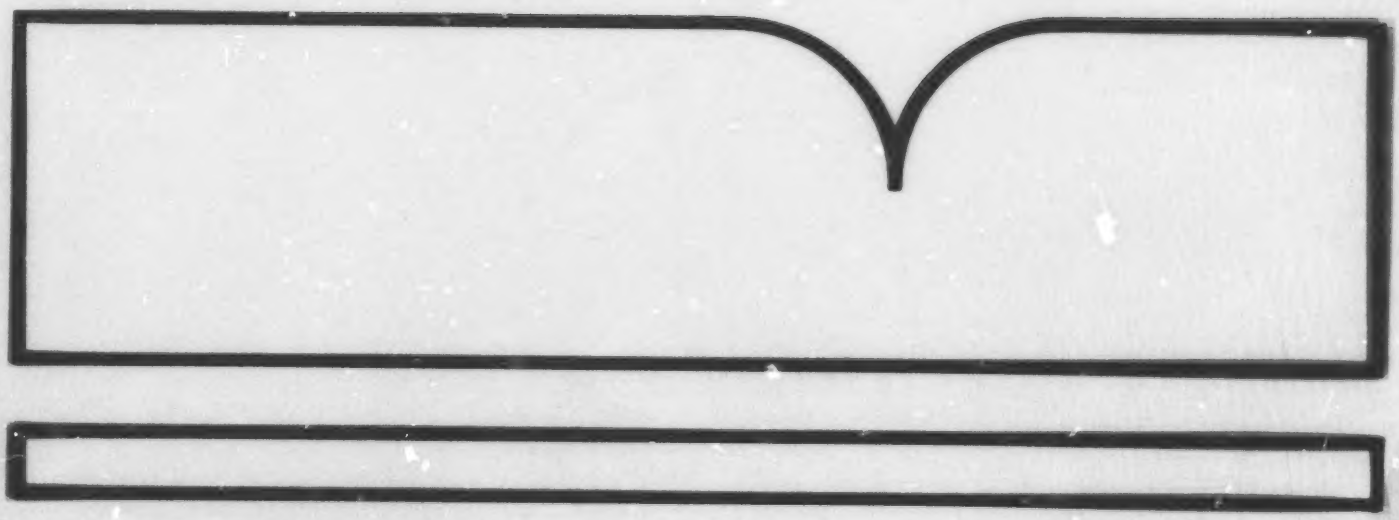

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16. ABSTRACT

An automated analysis of electrocardiographic (ECG) waveforms, based on a precise one-dimensional analysis of features within a generalized computer-enhanced ECG waveform, has been developed in our laboratory. ECG signals are monitored, amplified, and recorded using standard techniques. The recorder output signal is distributed to a microcomputer system. Software developed for the microcomputer slows the signal playback rate and permits operator review of the slowed signal for arrhythmia analysis. The analysis program identifies and superimposes 10-40 individual ECG complexes, depending on the heart rate, and generates an "ensembled" waveform. Operator interaction permits delineation of specific points on the displayed waveform and calculation of heart rate and duration of components within the ECG complex. The primary advantages of this system include (1) extensive automation—computer support decreases analytical time, increases precision, and permits rapid screening of large numbers of animals; (2) enhanced sensitivity—the use of functional parameters should provide a more sensitive index of toxicity than morphological parameters; (3) broad utility—this system provides the capability to utilize a variety of animals, both anesthetized and unanesthetized, ranging in age from fetuses to geriatrics, and permits studies of block as well as longitudinal design; and (4) ease of replication—standardization of equipment and techniques facilitates replication by other laboratories.

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A COMPUTER-ASSISTED ELECTROCARDIOGRAPHIC ANALYSIS SYSTEM: METHODOLOGY AND POTENTIAL APPLICATION TO CARDIOVASCULAR TOXICOLOGY

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An automated analysis of electrocardiographic (ECG) waveforms, based on a precise one-dimensional analysis of features within a generalized computer-enhanced ECG waveform, has been developed in our laboratory. ECG signals are monitored, amplified, and recorded using standard techniques. The recorder output signal is distributed to a microcomputer system. Software developed for the microcomputer slows the signal playback rate and permits operator review of the slowed signal for arrhythmia analysis. The analysis program identifies and superimposes 10-40 individual ECG complexes, depending on the heart rate, and generates an "ensembled" waveform. Operator interaction permits delineation of specific points on the displayed waveform and calculation of heart rate and duration of components within the ECG complex. The primary advantages of this system include (1) extensive automation—computer support decreases analytical time, increases precision, and permits rapid screening of large numbers of animals; (2) enhanced sensitivity—the use of functional parameters should provide a more sensitive index of toxicity than morphological parameters; (3) broad utility—this system provides the capability to utilize a variety of animals, both anesthetized and unanesthetized, ranging in age from fetuses to geriatrics, and permits studies of block as well as longitudinal design; and (4) ease of replication—standardization of equipment and techniques facilitates replication by other laboratories.

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INTRODUCTION

Exposure to toxic substances often produces alterations in heart rate (HR), heart rhythm, and electrocardiographic (ECG) waveform parameters. These changes may occur acutely following exposure to such diverse substances as carbon monoxide, digitalis, epinephrine, arsenic, and organophosphate pesticides (Klaasen, 1980a, b; Lucchesi, 1977a, b; Katz, 1977). Permanent alterations may develop as a consequence of myocardial damage or infarction subsequent to exposure to harmful agents, or as a result of exposure to teratogenic agents during organogenesis (Bruce and Irving, 1978; Grabowski and Payne, 1980; Hurst et al., 1978; Marriott and Myerburg, 1978; Sokolow and McIlroy, 1977; Wenger, 1978). Analyses of such physiological changes may provide a sensitive index of the degree of toxicity sustained. In the past, much of the information obtainable from detailed analyses of ECG changes has been largely ignored in toxicological studies due to the imprecision and tedium associated with manual analytical techniques. However, the ready availability of low-cost microcomputers has significantly enhanced the development of automated systems designed to rapidly process these data. Such systems would be beneficial to investigators in more general toxicological fields, as well as to those specifically studying the effects of agents on the cardiovascular system. The purpose of this report is threefold: (1) to describe a computer-assisted ECG analysis system that has been developed and tested in our laboratory; (2) to present general examples of the types of data obtained; and (3) to discuss the advantages, disadvantages, and appropriate applications of this system. Data illustrating specific applications of this system will be presented in subsequent reports.

METHODS

General

The computer-assisted electrocardiographic analysis system described here was originally developed to permit rapid screening of potentially toxic substances during the perinatal period using a variety of animal models. While the instrumentation employed and the protocols followed in this laboratory are presented, it is emphasized that few, if any, of the specific components or procedures are critical and multiple substitutions are possible.

Several species of animal models (mouse, rat, hamster, and guinea pig) at various ages from fetus through adult have been used to evaluate this system. In addition, postnatal animals have been monitored either anesthetized or unanesthetized, as well as restrained or free-ranging. The specific methodology employed is presented in the legend of each illustrative example.

The versatility of the system depends in part on the capability of obtaining a stable signal free of electrical noise. To enhance signal pick-up, slight procedural modifications have been incorporated according to the species, age, and state of anesthesia of the animal model. These modifications are summarized in Table 1. Electrodes are positioned on the ventral surface at the juncture of the extremities to approximate the standard human ECG limb positions of left arm, right arm, left leg, and right leg, with the latter serving as the grounded electrode. The electrodes are positioned on the trunk rather than on the limbs in order to increase the signal strength and decrease baseline artifact due to drift and limb movement.

Components

The specific components utilized in this system as well as the manufacturers and functions are summarized in Table 2. The arrangement of these components is shown in Fig. 1. All equipment is commercially available.

Operation

Briefly, the electrocardiographic signal is obtained by means of either surface or subcutaneous electrodes, as already indicated, and is input directly to the chart recorder. The signal is amplified and filtered as necessary to provide an optimal configuration for compatibility with the analysis program. The primary criteria that determine compatibility

TABLE 1. Modifications to Experimental Procedure According to Species, Age, and State of Anesthesia of Animal Model

Animal model	Type of electrode	Placement
Exteriorized fetus	Ag/AgCl ball electrode, with conducting gel (In Vivo Metrics, Healdsburg, Calif.)	Skin surface
Anesthesized rodent	Platinum needle electrode, Model E2B (Grass Instrument Co., Quincy, Mass.)	Subcutaneous
Unanesthesized, restrained, or free-ranging rodent	Platinum needle electrode, Model E2B (Grass Instrument Co., Quincy, Mass.)	Subcutaneous, held in place with one or two sutures, electrode wires secured out of reach of animal on dorsal surface
Unanesthesized, exercising dog	Gold-plated disk electrode, Model E4G (Grass Instrument Co., Quincy, Mass.)	Subcutaneous, held in place with one or two sutures, electrode wires secured out of reach of animal on dorsal surface

TABLE 2. Instrumentation Used in Computer-Assisted Electrocardiographic Analysis System

Instrumentation	Manufacturer	Function	Comment
Thermal recording system, model 7758B	Hewlett-Packard Co., Waltham, Mass.		Capability to monitor multiple signals (1-8)
Bioelectric amplifier, model 8811A		1. Provides amplification for original signal 2. Permits low/high frequency noise filtration, as necessary 3. Provides standardization voltage signal 4. Provides capability of rapidly switching to alternate lead systems	
Video display screen, model 78309A		Provides capability of visually monitoring processed signal in real time or during tape replay	
Thermal tip chart recorder, model 7758A		1. Provides permanent chart record of data in real time 2. Provides capability to reproduce data on chart during tape replay	
Cassette recorder, model R-61	TEAC Corporation, Tokyo, Japan	1. Provides permanent, inexpensive storage for processed analog signal 2. Provides signal playback capability	Capability to record and play back multiple FM signals (1-4)
Microcomputer System			
Display terminal (CRT), model ADM-3, with Tektronics Plot 10 capability	Lear Siegler, Anaheim, Calif.	1. Provides capability for slow-motion review of digitized signal 2. Provides capability for operator decisional input during analysis	
Dual disk drives	Lobo Drives, Goleta, Calif.	1. Loads analysis software program into computer 2. Provides data handling and storage capability	Uses 8-in floppy disks
Central processing unit (CPU), model ZILOG Z 80A	Tei, Inc., Houston, Tex.	Performs computations, etc. for analysis	
Analog-to-digital converter, model AD ADC80	Analog Devices, Norwood, Mass.	Converts analog tape signal to digital data	
Printer (PRT), model 810 with graphics capability	Texas Instruments, Inc., Houston, Tex.	Provides hard copy of data summary to include graphical representation of ECG waveform	

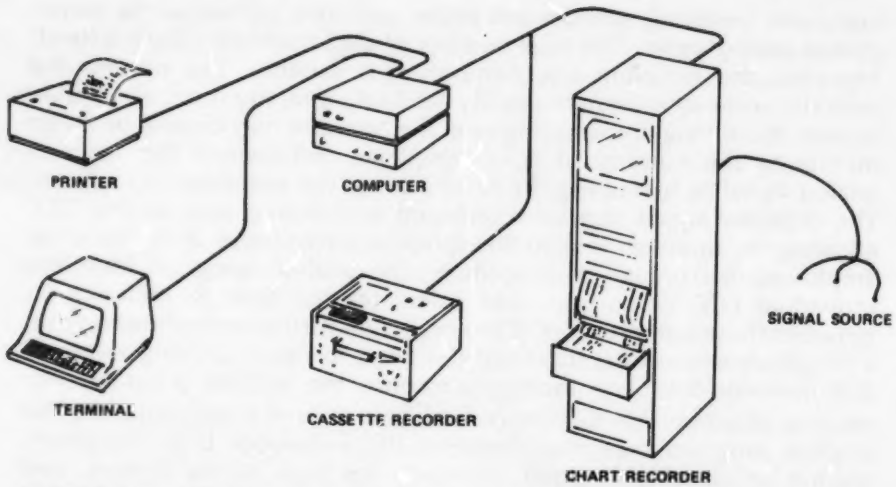


FIGURE 1. Diagram of instrumentation used in computer-assisted electrocardiographic system illustrating component interconnections. See text and Table 2 for detailed description of individual components.

are stability of baseline, minimal noise level, and the presence of a repetitive feature with either a positive or negative amplitude sufficiently distinguishable from baseline. The conditioned signal may be visually monitored on the recorder display screen and/or permanently reproduced on the chart paper. The analog output of the chart recorder is distributed to both the cassette recorder and the microcomputer system. The cassette recorder permits recording of the conditioned analog signal and provides inexpensive, permanent storage capability, as well as the facility for delayed playback and analysis. The microcomputer system that provides the rapid data-handling capability consists of an interactive display terminal (CRT) with graphics capability, a microcomputer (CPU) with 8-in dual disk drives, and a dot-matrix printer (PRT) with graphics capability.

The computer program that analyzes the ECG uses an ensembled beat technique that was previously developed to analyze cardiac performance during exercise stress (Petrovick et al., 1980). Briefly, this technique overlays multiple ECG waveforms to generate an averaged signal. The computer program permits operator interaction at selected points within the program, and provides for multiple levels of analysis. Some of the operational aspects and features of this program are summarized as follows. The conditioned analog signal may be input to the microcomputer either directly from the chart recorder or during playback from the cassette recorder. By means of an analog-to-digital converter, the

computer uniformly samples and stores a discrete portion of the conditioned analog signal. The total number of digital sample values is fixed; however, the sampling rate (samples/s) is variable. This permits the operator some discretion to modify the final signal to a more acceptable format. By varying the sampling rate, the operator may choose between increasing the number of ECG complexes included in the sampled analog signal or increasing the resolution of the individual complexes. The digitized signal may be monitored at a slowed rate on the CRT, allowing the operator to scan the signal for arrhythmias. By means of an amplitude-discrimination procedure, the analysis program identifies individual ECG complexes, and calculates the time in milliseconds between these complexes (R-R interval). As a further arrhythmia screen, a simple three-step statistical test designed to reject outlying values of R-R intervals has been incorporated into the analysis program. The mean of all acceptable R-R interval values is utilized to calculate HR. The analysis program then superimposes the individual ECG complexes around an identifiable point, generally the peak of the R-wave, and displays the resultant ensembled waveform on the CRT. Depending on the sampling rate and signal stability, between 10 and 40 individual ECG complexes will usually be ensembled. The operator interacts with the analysis program to delineate specific points on the displayed ensembled waveform. The variation of the analysis program used (e.g., either six or seven points identified) is dependent on the species and age of the experimental animal model. For fetal and young rats (< 20 d), as well as for larger animal models, the ECG closely approximates a human ECG, and the following six points are identified: (1) beginning of P-wave; (2) end of P-wave; (3) beginning of QRS complex; (4) end of QRS complex; (5) beginning of T-wave; and (6) end of T-wave. An idealized human ECG waveform illustrating cursor placement and interval identification using these six designated points is shown in Fig. 2. The ECG waveforms of postweanling and adult rats exhibit several unique features that distinguish them from human ECG waveforms and preclude analysis according to conventional techniques: namely, the postweanling or adult rat ECG is characterized by a high HR, a sloping baseline, an absence of a distinct S-T segment, and a shortened T-P interval (Driscoll, 1981; Detweiler, 1981). The analysis program, specifically the number and placement of the cursors, has been modified to accommodate these features of the rat ECG. Thus, for a postweanling or adult rat ECG, the following seven points are delineated: (1) beginning of P-wave; (2) end of P-wave; (3) beginning of QRS complex; (4) nadir of S-wave; (5) end of QRS complex; (6) peak of T-wave or αT-point; and (7) beginning of subsequent P-wave. These points where chosen for their analytical utility as well as their ease of identification and represent a compromise between standard human clinical parameters and parameters unique to

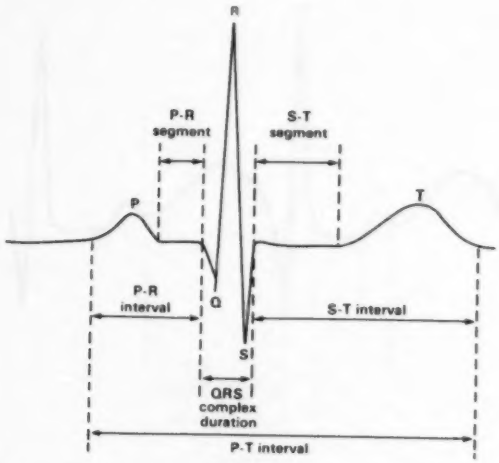


FIGURE 2. Diagram of human electrocardiographic waveform illustrating individual features and cursor placement. Single capital letters denote the individual waves of the electrocardiographic complex. Intersection of dashed lines with waveform represent position of cursor placement. Resultant interval measurements and segment lengths are shown as double-headed arrows between dashed lines.

the rat ECG. A typical ECG waveform from an adult rat illustrating the position of the cursors is shown in Fig. 3. Using the designated points obtained with either the six- or seven-cursor protocol, the analysis program calculates the duration, in milliseconds, of appropriate intervals and features within the generalized complex. These data and the ensembled waveform are printed on a summary sheet. A typical data summary sheet from an adult rat is presented in Fig. 4. As a final step, the analysis program transfers and stores all data on a second magnetic disk for consolidation and subsequent statistical analysis utilizing automated procedures (SAS Institute, 1982) on an in-house mainframe computer.

RESULTS

Illustrative examples of data summary sheets from several studies are presented in Figs. 4, 5, and 6. Specific examples have been selected to clarify and highlight features of the analysis system rather than to emphasize experimental results, which will be presented in subsequent publications. Relevant experimental details and noteworthy comments have been included in an expanded legend accompanying each figure.

Typical data from an adult rat are presented in Fig. 4. Cursors have been positioned using the modified program as previously described. General explanatory information regarding the data summary sheet,

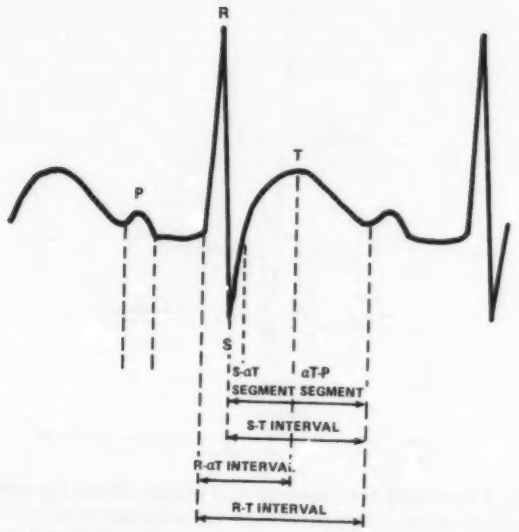


FIGURE 3. Diagram of electrocardiographic waveform of adult rat, illustrating differences from human electrocardiogram and modifications adopted regarding number and placement of cursors. Single capital letters denote the individual waves of the electrocardiographic complex. Intersection of dashed lines with the waveform indicate position of cursor placement. Interval measurements and segment lengths are shown as double-headed arrows between dashed lines. Only the interval calculations that differ from those of Fig. 2 are shown. Note: Waveform shows characteristic decreasing baseline, absence of S-T segment, and rapid heart rate, indicated by encroachment of subsequent P-wave on terminal portion of T-wave.

such as demarcation of optional points for early termination of the analysis program, has been noted.

Initial analog and ensembled waveforms of both control and Trypan blue-exposed neonatal rats from a teratology study are shown in Figs. 5 and 6, respectively. Examination of the original signal with respect to the ensembled waveform illustrates the capability of the system to reduce electrical and artifactual noise imposed on the ECG signal. In addition, these particular animals were selected from the same study to demonstrate the comparative capabilities of this system.

The analysis program is operator-oriented and was designed to be both rapidly learned and readily utilized. Presentation of data and information during analysis is limited to essential items, and operator interaction is solicited only when necessary to maintain system flexibility and decrease the time of analysis. Incorporation of operator prompts further decreases errors and speeds analysis time. The time required for an inexperienced operator to attain a level of competence sufficient to conduct independent analyses is short, typically 2 h or less. The average time required by a skilled operator to completely analyze an ECG using this system is approximately 3-4 min.

NUMBER OF
BEATS ENSEMBLED =23 (A)

ECG IDENTIFICATION:
TET TEST, 3JUNE83, NEM, #1, 6MG/KG, F, 112, 1700, 230.7, LII, CON (B)

ARRHYTHMIAS:
SLIGHT BREAK IN R-WAVE (C)

SAMPLE RATE: 1900 SAMPLES PER SECOND
SAMPLES COLLECTED: 10000
TOTAL SAMPLE TIME: 5 SEC

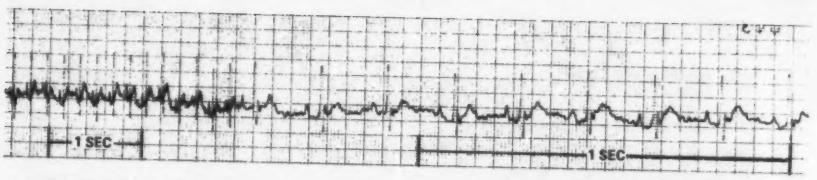
HEART RATE	291 BPM (D)	
R-R INTERVAL	206.01 MSEC	203.16/ 208.95 MIN/MAX (E)
P-T INTERVAL	205.79 MSEC	
P-R INTERVAL	46.84 MSEC	
R-aT INTERVAL	26.32 MSEC	
R-T INTERVAL	158.95 MSEC	
S-T INTERVAL	145.79 MSEC	
P-WAVE DURATION	17.37 MSEC	
QRS COMPLEX DURATION	15.26 MSEC	
T-WAVE DURATION	143.68 MSEC	
P-R SEGMENT LENGTH	29.47 MSEC	
S-T SEGMENT LENGTH	2.11 MSEC	
S-aT SEGMENT LENGTH	13.16 MSEC	
aT-P SEGMENT LENGTH	132.63 MSEC (D)	

TET TEST, 3JUNE83, NEM, #1, 6MG/KG, F, 112, 1700, 230.7, LII, CON

FIGURE 4. Data summary sheet obtained from 112-d-old female rat prior to intraperitoneal injection of triethyltin at 6 mg/kg. Rat was anesthetized with 35 mg/kg sodium pentobarbital (Nembutal, Abbott Laboratories, Chicago, Ill.). Animal weight was 230.7 g. ECG lead monitored was lead II. (A) Number of individual electrocardiographic complexes ensembled. (B) Space provided for operator identification of study and experimental animal. (C) Space provided for operator comments following slow-motion review of digitized signal. (D) Optional points for termination of analysis. (E) Average as well as minimum and maximum values of R-R interval, to provide information regarding variability of intervals. All R-R interval values are listed in the complete printout.

DISCUSSION

The ability to rapidly analyze electrocardiographic signals for changes in HR, HR variability, heart rhythm, and waveform parameters in response to exposure to harmful agents is potentially beneficial to



NUMBER OF BEATS ENSEMBLED =21

ECG IDENTIFICATION:
CONTROL, RAT, 10D, 20.7G, UNANESTHETIZED, LEAD II

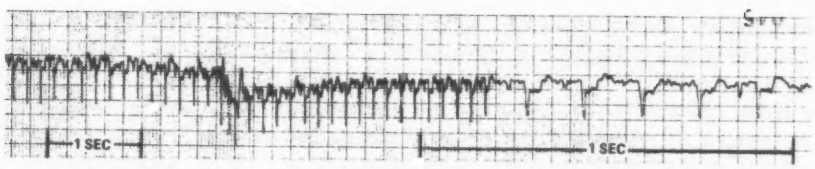
ARRHYTHMIAS:
NOISE, MOTION

SAMPLE RATE: 2500 SAMPLES PER SECOND
SAMPLES COLLECTED: 10000
TOTAL SAMPLE TIME: 4 SEC

HEART RATE	344 BPM
R-R INTERVAL	174.60 MSEC 168.80/ 178.00 MIN/MAX
P-T INTERVAL	114.80 MSEC
P-R INTERVAL	37.60 MSEC
Q-T INTERVAL	77.20 MSEC
S-T INTERVAL	59.20 MSEC
P-WAVE DURATION	16.40 MSEC
QRS COMPLEX DURATION	18.00 MSEC
T-WAVE DURATION	46.00 MSEC
S-T SEGMENT LENGTH	15.20 MSEC
P-R SEGMENT LENGTH	21.20 MSEC

CONTROL, RAT, 10D, 20.7G, UNANESTHETIZED, LEAD II

FIGURE 5. Electrocardiographic rhythm strip and data summary sheet obtained from 10-d-old untreated rat in control group of teratology study. Rat was unanesthetized and restrained. Animal weight was 20.7 g. ECG lead monitored was lead II. Note: The substantial electrical noise artifact of the analog signal is significantly reduced by the ensembling process.



NUMBER OF
BEATS ENSEMBLED =23

ECG IDENTIFICATION:
TREATED, RAT, 10D, 19.5, UNANESTHETIZED, LEAD II

ARRHYTHMIAS:
NOISE, INVERTED COMPLEX

SAMPLE RATE: 2500 SAMPLES PER SECOND
SAMPLES COLLECTED: 10000
TOTAL SAMPLE TIME: 4 SEC

HEART RATE	374 BPM
R-R INTERVAL	160.42 MSEC 156.80/ 163.60 MIN/MAX
P-T INTERVAL	134.00 MSEC
P-R INTERVAL	46.40 MSEC
Q-T INTERVAL	87.60 MSEC
S-T INTERVAL	67.60 MSEC
P-WAVE DURATION	14.80 MSEC
QRS COMPLEX DURATION	20.00 MSEC
T-WAVE DURATION	50.00 MSEC
S-T SEGMENT LENGTH	17.60 MSEC
P-R SEGMENT LENGTH	31.60 MSEC

TREATED, RAT, 10D, 19.5, UNANESTHETIZED, LEAD II

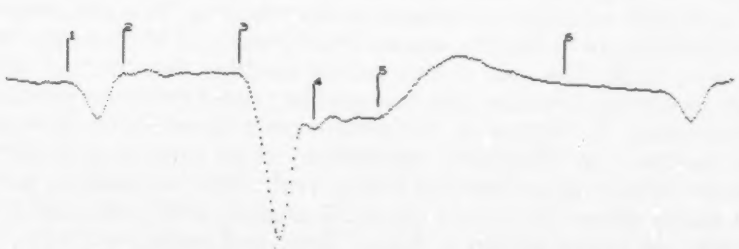


FIGURE 6. Electrocardiographic rhythm strip and data summary sheet obtained from 10-d-old rat exposed *in utero* to teratogenic agent. Mother was injected intraperitoneally on d 9 of gestation with 1 ml of a 1% solution of Trypan blue dye. Rat was unanesthetized and restrained. Animal weight was 19.5 g. ECG lead monitored was lead II. Note: (1) The substantial artifact due to electrical noise and animal movement in the analog signal is significantly reduced by the ensembling process. (2) The software provides the capability to trigger on a negative deflection as well as on a positive deflection. (3) The sampling rate has been modified to permit incorporation of the subsequent P-wave. (4) Identical experimental conditions allow comparison of aberrant complex of treated animal with normal complex of control animal (Fig. 5).

toxicologists (Budden et al., 1981; Detweiler, 1981). Changes in these parameters are often early indicators of acute toxic insult (Katz, 1977; Klaasen, 1980a,b; Wenger, 1978). Furthermore, cardiac alterations resulting from chronic administration of suspected cardiotoxicants may provide insight to concommitant morphological changes (Lucchesi, 1977b; Marriott and Myerburg, 1978; Watkinson et al., 1983). Monitoring such changes in functional parameters under physiological conditions should provide an additional sensitive index of toxicity that will complement results obtained exclusively from postmortem data. The computer-assisted ECG analysis system described here provides the capability of monitoring and rapidly analyzing these parameters using a variety of animal models over a wide range of experimental conditions. This system should prove useful for general toxicological studies, as well as for routine screening and diagnostic procedures.

Advantages

The primary advantages of this system include (1) extensive automation, (2) enhanced sensitivity, (3) broad utility, and (4) ease of replication.

Automation. The extensive automation gained through computer support facilitates detailed ECG analysis while substantially decreasing analytical time. The analysis program permits interaction at crucial points to ensure the highest possible accuracy. Computer processing and ensembling of the analog signal allow more precise determination of intervals and inflection points, while computer calculations and data printout save time and eliminate transcription errors. As a further benefit, the increase in analytical speed and precision gained through computer support tacitly encourages the use of greater numbers of animals per study, thereby improving overall statistical power.

Sensitivity. The enhanced sensitivity is attributable to the measurement and use of physiological parameters and experimental conditions. This is especially relevant with regard to determining the acute response following exposure to harmful agents (Watkinson and Millicovsky, 1983; Watkinson, 1985). The use of this system enables detection of subtle changes in cardiac function that may precede overt reactions produced at higher doses. Furthermore, this system permits extension of experimental control and diagnostic capabilities when used in conjunction with other physiological measurements, and when followed by pathological examination. By combining ECG analysis with such additional parameters as blood pressure, blood flow, and respiratory rate, it is possible to more accurately describe cardiovascular function and cardiac response.

Utility. The extensive utility of this system is an inherent function of the original design characteristics and constitutes a third major advantage. Developed primarily as a screening procedure capable of supporting a broad spectrum of analytical applications, this system provides

generous flexibility with regard to animal models, experimental protocols, and experimental design.

The choice of animal model is limited only by the capability of monitoring and amplifying the ECG signal. To date, this system has been tested on several different species (mouse, rat, hamster, and guinea pig) over a developmental range from fetal to geriatric. Signal strengths—e.g., the maximum amplitude of the R-wave—have ranged from approximately 40 μV in a 17-d exteriorized rat fetus to over 1 mV in an adult rat.

Experimental protocols have utilized both lightly anesthetized and restrained animals, as well as animals more deeply anesthetized in conjunction with surgical procedures. Experiments have also been conducted on unanesthetized, unrestrained animals. Thus far, all animals monitored with the present system have been studied under resting or control conditions. However, past studies that monitored HR and ECG of dogs with previously implanted electrodes while running on a treadmill have demonstrated the feasibility of using this system during studies in which the additional stress of exercise has been imposed (Watkinson et al., 1979). As a further refinement, this system could be used with radiotelemetry instrumentation. This would permit monitoring of ECG waveforms on unanesthetized, free-ranging animals without the complications of attached leads and cables or of human presence.

The analysis program incorporates several features that further enhance the versatility of the system. The operator may choose among several levels of analysis, ranging from a rapid survey of HR to an extensive determination of ECG intervals (Fig. 4). Another significant advantage of the ensembling procedure is its filtering effect and noise suppression capability. The algebraic summation process inherent in the ensembling procedure serves to reinforce consistent signals, such as ECG waveforms, while eliminating random electrical noise or movement artifact (Figs. 5 and 6). This capability extends normal monitoring conditions and makes this system particularly suitable for use with experimental protocols characterized by low signal/noise ratios, such as the low-strength signals of fetal animals or the high-noise-artifact signals that accompany movement in unanesthetized animals.

The versatility of this system is particularly apparent in the area of experimental design. The ease of sampling and the atraumatic, noninvasive experimental approach permit multiple samples from individual animals over varying time periods. This favors both block and longitudinal experimental designs and permits the study of chronic as well as acute effects of suspected agents, with each animal serving as its own control. Furthermore, it is possible to monitor the progression of development of toxic effects in the same animals.

Replication. As a final advantage, this system facilitates replication by other laboratories through standardization of equipment, techniques, and protocols. All equipment is commercially available, relatively inex-

pensive, and easily duplicated. The techniques and protocols followed are uncomplicated and readily modified. The permanent storage and easy retrieval of data further encourages comparison. The utilization of similar standardized procedures among laboratories should enhance consistency and replicability in cardiovascular toxicological testing.

Disadvantages

The primary disadvantage of this system concerns the limitations on the analysis of original analog data imposed by the software. The resultant product of the ensembling process precludes rigorous assessment of individual ECG complexes as well as overall heart rhythm. This is a purposeful limit that represents the costs of our methodological approach, and several compensatory measures have been incorporated. This limitation is partially offset by the capability of slow-motion review of the digitized signal. In addition, the variability of R-R intervals may be easily determined from the computer printout that lists the value of all individual intervals and the standard deviation of the mean of all intervals. The printout also indicates the minimum and maximum intervals and which intervals, if any, were rejected as outlying values. As a final precautionary measure, the original analog signal is retained on both magnetic tape cassette and chart recorder paper for subsequent review for these or additional parameters.

Potential Applications

Detailed one-dimensional analysis of the ECG using the system described here has a variety of potential applications in toxicology, as well as in teratology. It is particularly useful as a routine screening procedure for acute cardiovascular toxicity, thus serving to identify substances that merit further study. Other tested uses include the monitoring of maternal animals during teratological studies (Watkinson and Millicovsky, 1983a), longitudinal analysis of chronic or developmental effects (Watkinson et al., 1983), and assessment of the interaction of one or more agents with other substances or experimental conditions (Watkinson, 1985). The wide variety of animal models, potential substances, routes of administration, and interactive possibilities of this system insure a multiplicity of experimental designs tailored to specific individual needs.

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